Citation Index — Cover Page

EXHIBIT A — Oliva et al. (2020), BMJ Table Excerpt

ID	Source	Description
Exh. A	BMJ 368, m283	Oliva et al. (2020): estimated hazard ratio of approximately 6.77 for overdose or suicide death among patients whose opioid treatment was stopped after more than 400 days, relative to those who continued (associational, not causal); table excerpt (supports Policy Idea 5.1; Source 3)

Source: Oliva, E. M., et al. (2020). "Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans." BMJ, 368, m283. https://www.bmj.com/content/368/bmj.m283

Table 2 | Multivariable Cox non-proportional hazard regression model estimates for death from overdose or suicide in patients with an outpatient prescription for an opioid in fiscal year 2013 at the Veterans Health Administration

Variables	Parameter estimate	Standard error	Hazard ratio (95% CI)
Stopped treatment with opioids	1.91	0.06	—*
Stopped treatment with opioids×duration of last prescription for opioids (reference >400 days):			
≤30 days	−1.40	0.08	—*
31-90 days	−0.88	0.11	—*
91-400 days	−0.54	0.08	—*
Age (centered)	−0.02	0.002	0.98 (0.98 to 0.98)
Female sex	−0.57	0.08	0.56 (0.48 to 0.66)
Currently married	−0.63	0.04	0.53 (0.49 to 0.58)
Rural residence	−0.07	0.04	0.93 (0.86 to 1.01)
No of medical diagnoses	0.02	0.01	1.02 (1.01 to 1.04)
Substance use disorder (excluding nicotine)	0.91	0.05	2.48 (2.25 to 2.72)
Nicotine use disorder	0.03	0.04	1.03 (0.95 to 1.12)
Mental health disorder	0.43	0.04	1.54 (1.41 to 1.68)
Type of opioid treatment (reference tramadol only):			
Long acting	0.44	0.08	1.55 (1.33 to 1.82)
Short acting	0.15	0.06	1.16 (1.04 to 1.30)
Log maximum daily morphine mg equivalents	0.35	0.03	1.42 (1.34 to 1.50)

*Hazard ratios and associated 95% confidence intervals were not estimated for these variables as this was an interaction model. To better understand the interaction, the estimated hazard ratios for patients who stopped opioid treatment (with reference values for all other covariates) were 1.67 (≤30 days), 2.80 (31-90 days), 3.95 (91-400 days), and 6.77 (>400 days).

(>400 days). The pattern of increased numbers of deaths in the first three months after stopping treatment with opioids for all time periods was similar to figure 1 (top panel), but stabilization across the longer times (31-90, 91-400, and >400 days) was not as clear, with variability observed from three to 12 months after stopping treatment with opioids. The full life table descriptive data for figure 1 (bottom panel) are in appendix 5.

Discussion

Principal findings

In this quality improvement evaluation, we examined the risk of death from overdose or suicide associated with stopping treatment with opioids and length of treatment, in patients in the Veterans Health Administration prescribed opioids in fiscal year 2013. We found that the interaction between stopping treatment and length of treatment with opioids was associated with an increased risk of death from overdose or suicide the longer patients had been treated with opioids before stopping. The risk was pronounced in patients treated the longest. Also independently associated with a greater risk of death from overdose or suicide were not being married, male sex, having a diagnosis of a mental health or substance use disorder, medical comorbidities, and higher doses of opioids, similar to previous reports.[26-28 37] Our descriptive analyses showed the rise in the number of deaths from overdose or suicide in the months after stopping or starting opioid treatment, highlighting these vulnerable risk periods for patients. Our findings suggest that transitions (starting and stopping treatment) were associated with an increase in the risk for overdose and suicide for patients treated with opioids for any length of time, with increasing risk the longer patients were treated.

Comparisons with other studies

Previous studies focused mostly on smaller regional samples of patients treated with high doses of opioids or for long periods of time,[17 18] whereas our study used national data from the Veterans Health Administration and included all patients prescribed opioids. All patients exposed to opioids had an increased risk of death from overdose or suicide after starting or stopping treatment with opioids. Although patients treated with opioids for long periods (eg, >400 days in our evaluation) had the highest hazard ratios after stopping treatment, even those treated for up to 30 days had a rise in the risk of death after treatment was stopped (hazard ratio of 1.4 for death from overdose after stopping opioid treatment and 1.7 for death from overdose or suicide). Those treated with opioids for 31-90 days had a hazard ratio of 2.4 for death from overdose after stopping opioid treatment (2.8 for death from overdose or suicide). Our study reinforces the importance of the first three months after stopping opioid treatment, extending the high risk period from 77 days[17] to at least 100 days.

Priorities for future research

Future research should examine factors that might affect the risk or explain these findings. Glanz et al[16] found that high dose variability was a major predictor of increased risk for opioid overdose, and the rate of tapering has been hypothesized to moderate the risk after stopping treatment. This is concerning given that Mark et al[17] found that over half of patients treated with high doses of opioids for long periods of time suddenly stopped treatment with no reductions in dose (in one day), with 86% stopping within 21 days. The reasons for stopping treatment are also important. Demidenko et al[15] found evidence of suicidal thoughts and self-harm in patients with and without substance use disorders whose clinicians stopped their long term treatment with opioids. James et al[18] observed an increased risk of death from overdose in patients whose provider initiated stopping treatment although the findings were not statistically significant. In 77% of patients, at least one reason for stopping treatment came from the patients' providers whereas in only 18% had the patient decided to stop treatment. The risk of stopping treatment might reflect worsening pain, conflicts with or disengagement from providers, particularly during exacerbations of mental health disorders (eg, aberrant behaviors, substance misuse, or mania), symptoms related to withdrawal, or a combination of these factors.[15 38 39] Our findings suggest that future studies should include all patients prescribed opioids, not just those on long term treatment, and look at suicide behaviors in addition to outcomes of overdose.

Our evaluation did not focus solely on long term treatment with opioids or whether stopping treatment was voluntary, but our findings raise questions on whether evaluating stopping treatment with opioids in isolation is an effective population based strategy to reduce death from overdose or suicide. As we observed risks associated with starting and stopping treatment,

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Citation Index — Cover Page

EXHIBIT B — Tibbitts & Cowan (2021), NBER Working Paper 29139 Figure Excerpt

ID	Source	Description
Exh. B	NBER WP 29139	Tibbitts & Cowan (2021): estimates an association between the 2013 Opioid Safety Initiative and a divergence in veteran suicide trends relative to a civilian comparison group, concentrated among rural veterans (associational, not causal); figure excerpt (supports Policy Idea 5.1; Source 4)

Source: Tibbitts, J. C., & Cowan, B. W. (2021). "The Opioid Safety Initiative and Veteran Suicides." NBER Working Paper No. 29139. https://www.nber.org/papers/w29139

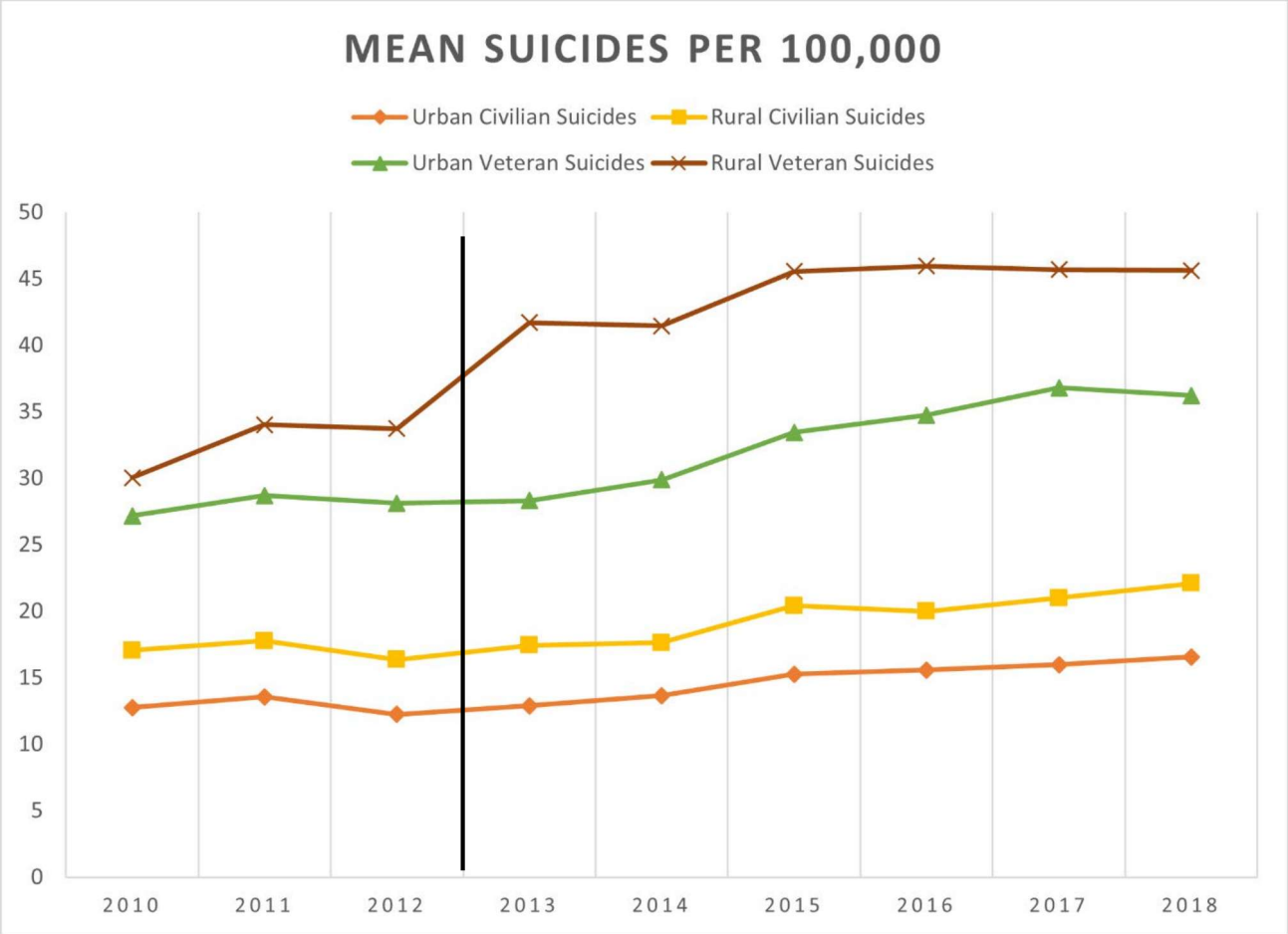

Figure 3 Average county-year suicide trend for veteran/military personnel and civilians, differentiated by urban-rural status, and weighted by total county population.

EXHIBIT C — EVIDENCE REVIEW SEARCH-TERM RECORD

Literature search strategies from the VA/DoD COT CPG Evidence Synthesis Report, Appendix A ("Literature Search Methods")

Source. Evidence Synthesis Report prepared by The Lewin Group / Center for Comparative Effectiveness Research (2017); literature searches conducted by ECRI Institute information specialists (Appendix A, production pp. 332–347 of 353). Obtained via VA FOIA Request No. 25-25897-F. Submitted with public comment, HHS FR Doc. 2026-11602 (91 FR 35221), in support of Policy Idea 5.1 (search-strategy transparency and gap audits).

Contents and authority. The authoritative record is the original Appendix A pages from the FOIA production (production pp. 332–347), reproduced here without alteration. Those pages set out the databases searched, the topic-specific controlled vocabulary and keyword terms, and the numbered EMBASE, Medline, and PsycINFO search statements for Key Questions 1–9. A submitter-prepared alphabetical word list may accompany these pages as an informal finding aid only; it is not a substitute for the original strategies and should not be relied upon in place of them. Appendix A itself distinguishes between the research-question descriptions in its "Concept" column and the terms actually executed in the controlled-vocabulary, keyword, and numbered-search-statement columns; any characterization of what was or was not searched should be read against the executed search statements, not the concept descriptions.

Relevance (factual observation, verifiable against the reproduced pages). Within the executed search vocabulary reproduced here, the medication term "buprenorphine" appears (Key Question 8 keyword column, production p. 335; EMBASE search set 64, production p. 342), and the strategies include numerous organ-system and adverse-event terms (for example, cardiac, cardiovascular, gastrointestinal, respiratory, liver, lung, osteoporosis, falls, insomnia). The strategies reproduced here do not include dental-outcome terms such as "dental," "tooth," "teeth," "caries," or "oral health."

Later regulatory context. On January 12, 2022, the U.S. Food and Drug Administration issued a Drug Safety Communication warning that dental problems — including tooth decay, cavities, dental abscesses or infection, tooth erosion, and in some cases total tooth loss — had been reported with transmucosal buprenorphine medicines (tablets and films dissolved under the tongue or against the inside of the cheek), including in patients with no history of dental issues; the FDA did not identify the same concern for other routes such as the skin patch or injection. This exhibit is offered to illustrate how outcome-coverage choices at the literature-search stage shape what evidence a guideline process can surface, and to support the recommendation that federally commissioned evidence-review search strategies be published and audited against adverse-event vocabularies in advance. It is not offered as an allegation of error, negligence, or misconduct.

FDA source: "FDA warns about dental problems with buprenorphine medicines dissolved in the mouth…," Jan. 12, 2022, https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-dental-problems-buprenorphine-medicines-dissolved-mouth-treat-opioid-use-disorder

Non-vocabulary limits applied in the strategies: publication years 2009–2016, English language, humans.

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Appendix A: Literature Search Methods

Resources Searched

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

Name	Search Dates	Platform/Provider
Agency for Healthcare Research and Quality (AHRQ)	Searched November 23, 2015	U.S. Department of Health & Human Services
Centers for Disease Control and Prevention (CDC)	Searched November 30, 2015	www.cdc.gov
Cochrane Library	Searched November 5, 2015	John Wiley & Sons, Ltd.
EMBASE (Excerpta Medica)	January 1, 2009 on	
Google	Searched November 23, 2015	www.google.com
Healthcare Standards (HCS)	Searched November 30, 2015	ECRI Institute
Medline	January 1, 2009 on	OVID Technologies, Inc.
National Guideline Clearinghouse (NGC)	Searched November 30, 2015	Agency for Healthcare Research and Quality (AHRQ)
National Institute for Health and Care Excellence (NICE)	Searched November 23, 2015	National Institute for Health and Care Excellence
PsycINFO	January 1, 2009 on	OVID Technologies, Inc.
PubMed (In-process, Publisher, and PubMedNotMeSH records)	Searched October 22, 2015 and January 11, 2016	National Library of Medicine (NLM)

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included feedback and recommendations from work group members and review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-specific Search Terms

The vocabulary presented in this table includes controlled vocabulary and free-text keywords for bibliographic database searches performed in EMBASE, Medline, and PsycINFO. Strategies for selected databases follow this table.

EMTREE, Medical Subject Headings (MeSH), PsycINFO, and Keywords

The strategies below are presented in Embase.com and OVID syntaxes. Embase.com was used to search for EMBASE (EMTREE) and Medline records. OVID was used to search PsycINFO.

Specific search strings were used to capture studies based on the key questions identified by the COT working group. Unique strategies were structured for each concept addressed by the key questions. These search results were further refined to capture specific study designs, publication types, date ranges, English language studies, and to exclude out-of-scope citations.

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Patient Population		
Chronic Pain	**EMBASE** 'chronic disease'/exp 'chronic inflammatory pain'/exp 'chronic pain' 'pain'/exp **MeSH** exp chronic disease/ exp pain/ **PsycINFO** Exp chronic illness/ exp chronic pain/ exp pain/	chronic Chronic adj3 pain* Chronic NEXT/3 pain* Long?term NEXT/3 pain* months pain weeks year*
Chronic Opioid Use	**EMBASE** 'analgesic agent'/exp 'codeine'/de 'drug therapy'/lnk 'fentanyl'/de 'morphine'/de 'narcotic agent'/exp 'narcotics'/exp 'narcotic drugs'/exp 'opiate'/de 'opiates'/exp **MeSH** Chronic pain/drug therapy exp analgesics, opioids exp narcotics **PsycINFO** exp analgesic drugs exp narcotics	Analgesic* COT 'chronic NEXT/1 opi* NEXT/1 therapy' 'chronic opi* therapy' codeine Fentanyl heroin Hydrocodone Hydromorphone Long?term Methadone months morphine narcotic* Opi* Oxycodone Oxycontin

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	exp narcotic drugs exp opiates	Oxymorphone percocet Tapentadol Tramadol Vicodin weeks Year*
KQ1 **Contraindications** What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing COT? • Active pursuit of compensation • Centralized pain conditions such as fibromyalgia • Chronic obstructive pulmonary disease • Cognitive impairment • Depression • Headache • GI motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome) • Immune status changes • Inability to participate in comprehensive treatment plan • Incarceration (history of) • Hepatic, renal, or pulmonary disease • Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed) • Osteoporosis • Personality disorders • Posttraumatic stress disorder • Sleep disorders • SUD (current or history of)—include specific disorders and appropriate key words in search • Suicidality • Traumatic brain injury • Use of medical marijuana • QT prolongation	**EMBASE** 'drug contraindication'/exp 'drug interaction'/exp 'drug safety'/exp **MeSH** analgesics, opioid/contraindications Polypharmacy/ **PsycINFO** Drug interactions/ Polypharmacy/ Safety/	Cardiovascular CNS COPD Compensation* Contraindication* depression Fibromyalgia gastrointestinal Headache* Heart immune Liver Lung Obstructive Osteoporosis (personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)) Post?traumatic stress PTSD Respiratory Sleep Substance adj2 (abuse OR misuse) Substance use disorder SUD Suicide suicidality TBI Traumatic brain

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
KQ2 **Risk factors for the continuum of misuse or OUD** What factors increase the risk of developing misuse or OUD when considering COT?	**EMBASE** 'analgesic agent abuse'/exp 'bullying'/exp 'opiate addiction'/exp 'opioid-related disorders'/exp 'risk'/exp 'sexual abuse'/exp **MeSH** 'bullying'/ 'domestic violence'/exp 'risk assessment'/exp 'substance-related disorders'/exp **PsycINFO** Exp addiction/ Exp at risk populations/ Exp codependency/ Exp drug abuse/ Exp drug addiction/ Exp drug overdoses/ Exp illegal drug distribution/ Exp risk assessment/ Exp risk factors Exp risk perception/	Abuse Addict* Assess* Bully Bullying dependency Disorder* Overdose* Predict* Risk* violence
KQ3 AND KQ4 **Effectiveness of COT** What is the comparative effectiveness of COT versus other treatment modalities? a. What is the comparative effectiveness of COT versus other treatment modalities for patients with a history of or current SUD? **Safety of COT** What is the safety of COT versus other treatment modalities? a. What is the safety of COT versus other treatment modalities for patients with a history of or current SUD?	**EMBASE** 'adverse drug events'/exp 'adverse drug reaction'/exp 'adverse drug reaction'/lnk 'patient safety'/exp 'prescription drugs'/exp 'side effect'/lnk 'side effect'/de 'treatment outcome'/de **MeSH** 'analgesics, opioid'/*adverse effects 'prescription drugs'/adverse effects 'quality of life' 'risk' 'side effect'/de 'treatment outcome' **PsycINFO** *quality of life/	Aberrant NEXT/3 behavior* Absence absent Abuse Accident* 'ade' Addict* adverse 'adverse drug events' Adverse NEXT/1 effect* Anxiety cardiac cardiovascular cognitive complication depression Diversion effective

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	"side effects (drug)"/ *treatment outcomes/ Drug overdose/*prevention & control	effectiveness Fall Falls Misuse Mood Outcome* Overdose 'pain relief' Pain NEXT/2 relief Pain NEXT/3 reliev* 'quality of life' QOL Safety 'side effect*' Sleep s
KQ5 **Effectiveness of different opioid formulations** What is the comparative effectiveness and safety of various opioid formulations? a. Immediate-release/short-acting opioids compared to extended-release/long-acting opioids b. Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c. Abuse deterrent formulations compared to non-abuse deterrent formulations d. Tramadol and other dual-mechanism opioids e. Buprenorphine f. Methadone	**EMBASE** 'short acting analgesic agent'/exp **MeSH** 'analgesics, short-acting' **PsycINFO** *drug therapy	Abuse-deterrent controlled 'controlled release' extended 'extended release' Formulation immediate 'immediate release' LA 'long?acting' Medication Medicine Pill* Prescription* SA 'short?acting' (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) Sustained
KQ6 **Added benzodiazepines** Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?	**EMBASE** 'antidepressant agent'/exp 'benzodiazepine' 'benzodiazepine derivative'/exp 'hypnotic sedative agent'/exp 'narcotic analgesic agent'/exp	Ambien 'anti depressant' Antidepressant* Anti-depressant' Benzodiazepine* 'eszopiclone'

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	'non prescription drug' 'prescription drug' **MeSH** 'patient safety' 'polypharmacy'/exp 'safety' **PsycINFO** exp analgesic drugs/ Exp anesthetic drugs/ Exp anticonvulsive drugs/ Exp antidepressant drugs/ Exp antiemetic drugs/ Exp antihistaminic drugs/ Exp antihypertensive drugs/ exp benzodiazepines/ exp cns depressant drugs/ drug therapy/sh *hypnotic drugs/ Insomnia.id. Major depression.id. Exp polypharmacy/ Schizophrenia.id. Exp sedatives/ Exp self medication/	Hypnotic* lunesta OTC 'over-the-counter' 'over the counter' prescription* polypharmacy psychoactive* sonata stimulant* 'z drug' 'z drugs' 'zaleplon' 'zolpidem'
KQ7 **Risk mitigation strategies** What is the comparative effectiveness of different risk mitigation strategies for patients either on COT or being considered for COT? a. Does this differ for patients with history of or current SUD? b. Does this differ for patients with mental health comorbidities? c. Does this differ for patients with medical comorbidities?	**EMBASE** 'opiate addiction'/exp 'patient education'/exp 'prescription drug diversion'/exp 'risk reduction'/exp 'substance abuse'/exp 'urinalysis'/exp **MeSH** 'contracts' 'drug monitoring' exp 'patient compliance'/ exp 'risk'/ **PsycINFO** exp addiction/ Exp client education/ exp drug abuse/ drug abuse.sh. exp drug addiction/	Abuse Addict* agreement 'call back' Call-back Compliance comply consent contract database diversion divert doctor Detect* Diversion Divert Misuse Monitor*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	opiates.id. exp monitoring/ exp patient compliance/ Exp prescription drugs/ Exp risk assessment/ Exp risk evaluation and mitigation strategy/ Exp risk perception/ Exp treatment compliance/	Naloxone NEXT/2 rescue office Pill NEXT/2 count physician primary Query Recall Risk* Screen* surveillance Test* Urin*
KQ8 **Treatment of OUD** What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a. Do outcomes vary by severity of OUD?	**EMBASE** 'acceptance and commitment therapy'/exp 'addiction'/exp 'analgesic agent abuse'/exp 'cognitive therapy'/exp 'drug abuse'/exp 'drug dependence'/exp 'narcotic analgesic agent'/exp 'narcotic dependence'/exp 'opiates'/exp 'opiate addiction'/exp 'psychotherapy'/exp 'support group'/exp **MeSH** 'analgesics, opioid'/exp 'cognitive therapy'/exp 'counseling'/exp 'motivational interviewing'/ 'narcotics'/exp 'substance abuse detection'/exp 'substance-related disorders'/exp **PsycINFO** exp addiction/ Exp adjunctive treatment/ Exp cognitive therapy/ Exp counseling/ exp drug abuse/ drug abuse.sh. exp drug addiction/ exp drug dependence/	aberrant Abuse Addict* Behavioral buprenorphine Cognitive Contingency 'contingency management' Counsel* counseling drug interview* methadone misuse motivation* naltrexone therapy treat* treatment

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	electrosleep treatment/ exp motivational interviewing/ exp opiates/ opiates.id. Exp prescription drugs/ Exp psychotherapy/ Exp support group/ Exp treatment/ Exp treatment compliance/ Exp treatment effectiveness evaluation/ Exp treatment outcomes/	
KQ9 **Tapering** What is the safety and effectiveness of different tapering strategies and schedules?	**EMBASE** 'analgesia'/exp 'clinical protocol'/exp 'dose response'/exp 'drug administration'.exp 'drug therapy'/lnk 'pain management'/exp **MeSH** 'clinical protocols'/exp 'drug administration schedule'/exp **PsycINFO** exp analgesic drugs/ Exp drug dosages/ Exp pain management/	Adjust* administration Decrease* Dose Dosing plan protocol Reduc* Schedule Strategy strategies Taper* Titrat*

EMBASE Conventions:

* (within or following a term) = truncation character (wildcard)

:ab = limit to abstract

:ab,ti = limit to abstract and title

NEAR/n = search terms within a specified number (*n*) of words from each other in any order

/exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

:it. = limit to publication type

:ti. = limit to title

EMBASE/Medline Search Strategies conducted using Embase.com Syntax

Set #	Concept	Search Statement
1	Chronic pain	'chronic pain'/exp OR (chronic OR 'long term') NEXT/2 pain*
2		'chronic inflammatory pain'/de OR (chronic NEXT/3 pain*):ab,ti.
3	Combine sets for chronic pain	1 OR 2
4	COT	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
5		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic*
6		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
7		Oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
8		'pain'/exp AND 'drug therapy'/lnk AND opi*
9	Combine sets for opioids	4 OR 5 OR 6 OR 7 OR 8
10	Combine with chronic	9 AND (chronic:ti OR 'cot':ti OR chronic NEXT/1 opi* NEXT/1 therapy OR longterm:ti OR 'long term':ti OR months:ab,ti OR year*:ab,ti)
11	Combine chronic pain with COT	3 AND 10
12	Contraindications (KQ1)	'drug contraindication'/exp OR 'drug interaction'/exp OR 'drug safety'/exp OR 'analgesics, opioid/contraindicaitons'
13		Compensation* OR contraindication* OR copd OR cardiovascular OR respiratory OR 'chronic obstructive' OR lung OR fibromyalgia OR headache* OR heart OR liver OR sleep OR osteoporosis OR cns OR immune OR gastrointestinal OR medic* NEAR/1 marijuana OR 'post-traumatic stress' OR ptsd OR 'traumatic brain' OR tbi OR 'substance use disorder' OR sud OR depression OR suicide OR suicidality OR (personality OR cognitive OR mental OR neuro*) NEXT/3 (disorder* OR disease* OR illness*)
14	Combine contraindications	12 OR 13
15	Combine contraindications with chronic pain and COT	11 AND 14
16	Risk of misuse (KQ2)	('opiate addiction'/exp OR 'analgesic agent abuse'/exp OR 'opioid-related disorders'/exp) AND ('risk'/exp OR risk*:ab,ti)
17		'risk'/exp OR (risk* AND (predict* OR assess*))
18		(opi* OR narcotic* OR hydrocodone OR vicodin OR oxycodone OR oxycontin OR percocet OR heroin OR methadone OR morphine OR codeine OR analgesic*) NEXT/2 (addict* OR abuse OR misuse OR disorder OR diversion)
19	History of abuse	'domestic violence'/exp OR 'sexual abuse'/exp OR 'bullying'/exp OR bully OR bullying OR (domestic OR spous* OR child* AND (abuse OR violence))
20	Risk of opioid addiction	17 AND (18 OR 19)
21	Combine risk sets	16 OR 20
22	Combine risk of misuse with chronic pain and COT	11 AND 21
23	Effectiveness and Safety of COT (KQs 3 and 4)	'adverse drug events' OR 'ade' OR overdose OR diversion OR misuse OR addict* OR abuse OR adverse NEXT/1 event OR adverse NEXT/1 effect* OR accident* OR absence OR absent OR falls OR fall OR depression OR anxiety OR mood OR sleep OR aberrant NEXT/3 behavior* OR complication* OR cardiovascular OR cardiac OR cognitive

Set #	Concept	Search Statement
24		'quality of life'/exp OR 'quality of life' OR qol OR pain NEXT/2 relief OR pain NEXT/2 reliev* OR 'pain relief'
25		'prescription drugs'/exp AND ('adverse drug reaction'/lnk OR 'side effect'/lnk)
26		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
27	Combine sets for safety	23 OR 24 OR 25 OR 26
28	Combine with chronic pain and COT	11 AND 27
29	Formulations (KQ5)	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
30		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
31		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
32		'pain'/exp AND 'drug therapy'/lnk AND opi*
33	Combine sets for opioids	29 OR 30 OR 31 OR 32
34		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) OR 'short acting analgesic agent'/exp OR (abuse-deterrant AND formula*)
35		33 AND 34
36		'opiate'/exp OR 'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de OR morphine OR oxycodone OR oxymorphone OR opi* AND (controlled OR sustained OR extended)
37	Opioid formulations	35 OR 36
38	Combine with chronic pain and COT	11 AND 37
39	Added benzodiazepines (KQ6)	'benzodiazepine derivative'/exp OR 'benzodiazepine' OR benzodiazepine* OR 'antidepressant agent'/exp OR 'hypnotic sedative agent'/exp OR 'narcotic analgesic agent'/exp OR 'benzodiazepine derivative'/exp OR 'zolpidem'/exp OR 'zaleplon'/exp OR 'eszopiclone'/exp
40		'zolpidem' OR 'zaleplon' OR 'eszopiclone' OR ambien OR lunesta OR sonata OR benzodiazepine* OR antidepressant* OR 'anti-depressant' OR 'anti depressant' OR stimulant* OR 'z drug' OR 'z drugs' OR hypnotic* OR psychoactive*
41		prescription* AND (otc OR 'over the counter') AND (multiple* OR added OR additional OR several OR concomitant)
42		'prescription drug'/exp AND 'non prescription drug'/exp OR 'polypharmacy'/exp
43	Combine medicine sets	38 OR 39 OR 40 OR 41
44		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
45	Combine with outcomes	42 AND 43
46	Combine with chronic pain and COT	11 AND 45

Set #	Concept	Search Statement
47	Risk mitigation for addiction (KQ7)	'opiate addiction'/exp OR 'substance abuse'/exp OR 'drug monitoring'/exp OR 'prescription drug diversion'/exp OR ((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol))
48		urin* NEXT/7 (screen* OR test* OR detect* OR anal* OR monitor*) OR 'urinalysis'/exp
49		pill NEXT/2 count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR naloxone NEXT/2 rescue
50		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
51		'patient education'/exp OR patient NEXT/3 (aware* OR educat*)
52		(office OR doctor OR primary) NEXT/3 (visit* OR appointment* OR check*)
53		'contracts'/exp OR opi* NEXT/5 (contract OR contracts OR agreement)
54		Risk* NEXT/7 (mitigate* OR reduc*) OR 'risk'/exp OR 'risk reduction'/exp OR 'risk evaluation and mitigation strategy'
55	Combine risk mitigation strategies	47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54
56	Combine with chronic pain and COT	11 AND 55
57	Treatment of OUD (KQ8)	addict* OR abuse OR misuse OR disorder AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol) OR 'opiate use disorder'
58		'opiate addiction'/exp OR 'analgesic agent abuse'/exp OR ('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp OR aberrant:ti OR aberrant:ab AND ('narcotic analgesic agent'/exp OR 'opiates'/exp OR opioid* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol OR analgesic*))
59		'psychotherapy'/exp OR 'cognitive therapy'/exp OR 'counseling'/exp OR 'acceptance and commitment therapy'/exp OR 'support group'/exp OR 'motivational interviewing'/exp
60		counsel OR counseling OR (cognitive OR contingency OR drug OR behavioral OR motivational) NEAR/2 (counseling OR therapy) OR 'contingency management' OR motivation* NEAR/1 interview* OR buprenorphine OR naloxone OR methadone
61	Combine opioid addiction set	57 OR 58
62	Combine counsel set	59 OR 60
63	Combine with chronic pain and COT	11 AND 61 AND 62
64	Tapering (KQ9)	'pain management'/exp OR 'analgesia'/exp AND ('drug administration'/exp OR 'clinical protocol'/exp)
65		'dose response'/exp OR ((dose OR dosing) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies))

Set #	Concept	Search Statement
66		(taper* OR decrease* OR reduc* OR adjust* OR titrat* OR dosing OR dose*) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies)
67	Combine tapering sets	64 OR 65 OR 66
68	Combine with chronic pain and COT	11 AND 67
69	Combine all final sets	15 OR 22 OR 28 OR 38 OR 46 OR 56 OR 63 OR 68
70	Apply limits	69 AND [2009-2016]/py AND [English]/lim AND [humans]/lim
71	Apply unwanted publication types	70 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
72	Apply trials hedge	71 AND (random*:ab,ti OR trial* OR control* OR cohort OR compar*:ab,ti OR prospective OR retrospective OR series OR review* OR study OR studies OR method* OR analysis OR systematic*:ab,ti)
73		71 AND ('clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'longitudinal study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/de OR 'comparative study'/exp OR 'methodology'/exp)
74		71 AND ('meta analysis'/de OR 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'outcomes research'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'systematic review'/de OR 'meta? analysis':ab,ti OR 'systematic review':ab,ti)
75	Combine	72 OR 73 OR 74

OVID Conventions:

* (within or following a term) = truncation character (wildcard)

.ab. = limit to abstract

ADJn = search terms within a specified number (*n*) of words from each other in any order

exp/ = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.ti,ab. = limit to title and abstract fields

PsycINFO Search Strategies Presented in OVID Syntax

Set #	Concept	Search Statement
1	Chronic pain	*exp chronic pain/ OR (exp pain/ AND (chronic OR long?term)) OR (exp chronic illness/ AND pain?)
2		Chronic adj3 pain?.ti,ab.
3	Combine	1 OR 2
4	COT	exp analgesic drugs/ or exp narcotics/ or exp narcotic drugs/ or exp opiates/

Set #	Concept	Search Statement
5		(opioid* or opiod* or opiate* or oposal or opon or narcotic*).mp. OR (morphine or codeine or fentanyl).mp.
6		(Oxymorphone or tapentadol or methadone or fentanyl or hydrocodone or oxycodone or codeine or morphine or hydromorphone or tramadol).mp.
7	Combine	4 OR 5 OR 6
8	Combine chronic pain and COT	3 AND 7
9	Contraindicaitons (KQ1)	(Contraindication or COPD or cardiovascular or respiratory or obstructive or lung or fibromyalgia or headache or heart or liver or sleep or osteoporosis or CNS or immune or gastrointestinal).mp.
10		(medic* adj1 marijuana).mp. or ("post?traumatic stress" or PTSD).mp. or traumatic brain.mp. or TBI.ti,ab. or (substance adj2 abuse).mp. or (substance adj2 misuse).mp. or (depression or suicide or suicidality).mp. or ((personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)).mp.
11		9 OR 10
12	Workers compensation	exp litigation/ or exp workers' compensation insurance/ or lawsuit.mp. or litigation.mp. exp insurance/ or insurance claim.mp. or exp disability evaluation/ or exp malingering/ or malingering.mp.
13		(worker adj2 compensation).mp. or litigation.ti. or lawsuit.ti. or claim*.ti. or disability*.ti. or compensation.ti. or malinger*.ti.
14	combine	11 OR 12 OR 13
15	Combine with chronic pain and COT	8 AND 14
16	Risk of misuse (KQ2)	Exp drug abuse/ or exp addiction/ or exp codependency/ or exp drug addiction/ or exp drug overdoses/ or exp illegal drug distribution/
17		16 AND (opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*).mp.
18		((opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*) adj2 (addict* or abuse or misuse or disorder* or diversion)).mp.
19		Risk*.mp. or exp risk assessment/ or exp risk perception/ or exp at risk populations/ or exp risk factors/
20		17 OR 18
21	Combine risk and abuse	19 AND 20
22	Combine with chronic pain and COT	8 AND 21
23	Effectiveness and Safety of COT (KQs 3 and 4)	exp "Side Effects (Drug)"/ or exp "side effects (treatment)"/ or exp "complications (disorders)"/
24		exp Suicide/ or exp Major Depression/ or exp Attempted Suicide/ or exp Drug Abuse/ or exp Drug Overdoses/ or exp Drug Addiction/ or exp Safety/ or overdose.mp. or adverse events.mp. or drug addiction.mp.
25		Exp pain management/ or (pain adj2 (reliev* or relief)) or exp Quality of Life/ or quality of life.mp. or exp treatment outcomes/ or outcomes.mp.
26		((adverse adj1 event*) or (adverse adj1 effect*) or (aberrant adj3 behavior*)).mp. or (overdose* or diversion or addict* or abuse or accident* or complication* or absence or absent or falls or fall or depression or anxiety or mood or sleep or cardiovascular or cardiac or cognitive).ab,ti.

Set #	Concept	Search Statement
27		((work or occupation* or job) adj3 (injur* or accident or absence or performance)).mp. or exp safety/ or exp occupational safety/ or exp accidents/ or exp job performance/ or exp employee absenteeism/ or exp cognitive processes/ OR exp cognitive impairment/
28		exp driving behavior/ or exp drivers/ or exp risk taking/ or exp risk perception/ or exp highway safety/ or exp motor traffic accidents/ or exp motor vehicles/ or exp transportation accidents/ or exp motor traffic accidents/ or (accident* or crash or collison or wreck).mp. or ((drive or driving or car* or traffic or vehicle*) and (safe* or accident* or crash* or wreck* or impair* or risk* or collison*)).mp.
29	Combine	23 OR 24 OR 25 OR 26 OR 27 OR 28
30	Combine with COT	7 AND 29
31	Formulations (KQ5)	(*drug therapy/ or (prescription* or medication or medicine or pill*).mp. AND opi*
32		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)).mp.
33		(formulation* or short?act* or long?act* or immediate or extended or controlled or sustained or abuse-deterrent or (abuse adj1 deterrent)).mp.
34		(opiate* or opioid).ti. and (formulation* or short?act* or long?act* or immediate or extended or controlled or sustained).mp.
35	Combine	(31 AND (32 OR 33)) OR 34
36	Combine with COT	7 AND 35
37	Added benzodiazepines (KQ6)	benzodiazepine*.mp. or exp benzodiazepines/
38		*hypnotic drugs/ or exp analgesic drugs/ or exp anesthetic drugs/ or exp anticonvulsive drugs/ or exp antiemetic drugs/ or exp antihistaminic drugs/ or exp antihypertensive drugs/ or exp benzodiazepines/ or exp cns depressant drugs/ or exp sedatives/ or exp antidepressant drugs/ or exp nonprescription drugs/ or exp self medication/ or exp prescription drugs/ or exp polypharmacy/
39		(insomnia or chronic pain or schizophrenia or major depression).id. and drug therapy.sh.
40		(zolpidem or zaleplon or eszopiclone or ambien or lunesta or sonata or benzodiazepine* or antidepressant* or anti-depressant* or stimulant* or 'z drug' or 'z drugs' or hypnotic* or psychoactive*).mp.
41		(over-the-counter or 'over the counter' or OTC).mp or (prescription* or prescribed).ab,ti. Or polypharmacy.mp.
42		((medication* or medicine) and (multiple or concomitant or several)).mp.
43	Combine	37 OR 38 OR 39 OR 40 OR 41 OR 42
44	Combine with chronic pain and COT	8 AND 43
45	Risk mitigation for addiction (KQ7)	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
46		((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
47	Combine opiate addiction or misuse	45 OR 46

Set #	Concept	Search Statement
48	Mitigation strategies	urin* adj7 (screen* OR test* OR detect* OR anal* OR monitor*) OR exp urinalysis/ or exp drug usage screening/
49		Count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR ('pill count' OR pill count).mp.
50		(naloxone adj2 rescue).mp.
51		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
52		Exp treatment compliance/ or (patient and (compliance or comply)).ab,ti.
53		((office OR doctor OR primary) adj3 (visit* OR appointment* OR check*)).mp. OR (exp opiates/ AND exp monitoring/)
54		Exp client education/ or patient education.mp. OR patient NEXT/3 (aware* OR educat*)
55		(opi* adj5 (contract OR contracts OR agreement)).mp.
56	Combine mitigation strategies	48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55
57	Risk	Exp risk assessment/ or exp risk perception/ or (risk* adj7 (mitigate* OR reduc*)).mp. or (risk evaluation and mitigation strategy).mp.
58	Combine addiction, mitigation, and risk	47 AND 56 AND 57
59	Combine addiction, mitigation, and risk with COT	7 AND 58
60	Treatment of OUD (KQ8)	((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
61	Opiate addiction or misuse	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
62		(exp drug abuse/ or exp drug dependence/ or exp drug addiction/ or aberrant.ti. or aberrant.ab.) and (exp opiates/ or opioid*.mp. or oxymorphone.mp. or tapentadol.mp. or methadone.mp. or fentanyl.mp. or hydrocodone.mp. or oxycodone.mp. or codeine.mp. or morphine.mp. or hydromorphone.mp. or tramadol.mp. or analgesic*.mp.)
63	Counseling	Exp psychotherapy/ OR exp cognitive therapy/ OR exp counseling/ OR exp support group/ OR exp motivational interviewing/ exp Adjunctive Treatment/ or exp Treatment Compliance/ or exp Treatment/ or exp Treatment Effectiveness Evaluation/ or (treat or treatment or therap* or counsel*s).ab,ti.
64		counsel OR counseling OR ((cognitive OR contingency OR drug OR behavioral OR motivational) adj2 (counseling OR therapy)) OR motivation* adj1 interview* OR (buprenorphine OR naloxone OR naltrexone OR methadone) OR contingency management.mp.
65	Combine addiction	60 OR 61 OR 62
66	Combine counseling	63 OR 64
67	Combine COT and addiction and counseling	7 AND 65 AND 66
68	Tapering (KQ9)	(exp analgesia/ or exp analgesic drugs/ or exp pain management/) AND exp drug dosages/
69		((dose or dosing) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.

Set #	Concept	Search Statement
70		(taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*).mp.
71		((taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.
72	Combine tapering sets	68 OR 69 OR 70 OR 71
73	Combine tapering and chronic pain and COT	8 AND 72
74	Combine all final sets	15 OR 22 OR 30 OR 36 OR 44 OR 59 OR 67 OR 73
75	Apply limits	limit 74 to (human and english language and yr="2009 - 2016")
76	Apply publication type limits	75 AND (trial* or study or studies or method* or review* or analysis or compar* or random* or systematic*).mp.
77		limit 75 to ("0100 journal" or "0110 peer-reviewed journal" OR “journal article”)
78		75 AND (exp clinical trials/ or exp cohort analysis/ or exp followup studies/ or exp longitudinal studies/ or ((compar* or comparison or comparative) and trial*).ab,ti.
79	Combine final sets	76 OR 77 OR 78

EXHIBIT D — EPIDEMIOLOGICAL ANALYSIS OF STATE-LEVEL BANS

Excerpts from a doctoral dissertation examining state-level bans and opioid-overdose mortality

Source. Blair, L. (2022). Investigating the relationships between socioeconomic status, kratom legislation, and the COVID-19 pandemic on opioid overdose mortality in the United States (doctoral dissertation, University of Louisville). Submitted with public comment, HHS FR Doc. 2026-11602 (91 FR 35221), in support of Policy Idea 3.2 and Section V, Source 5. Available via the University of Louisville Electronic Theses and Dissertations repository: https://ir.library.louisville.edu/etd/

Contents. The attached pages are reproduced from the dissertation without alteration, with passages highlighted by the submitter for reviewer convenience: (a) Table 3.1 — opioid-overdose death counts and crude rates per 100,000 by year for each state with kratom-banning legislation (Indiana, Vermont, Wisconsin, Arkansas, Alabama, Rhode Island; bold years mark ban implementation); (b) the Conclusion (p. 56); and (c) the Discussion (pp. 58–59). The highlighted passages carry the author's verbatim text; the summary below is paraphrased.

Relevance (paraphrased; see attached pages for verbatim text). Using an interrupted-time-series design, the dissertation examined opioid-overdose mortality before and after state-level kratom bans. After controlling for the pre-intervention trend, the author reports that five states (Indiana, Vermont, Wisconsin, Arkansas, and Alabama) had higher opioid-overdose death rates following ban implementation, while Rhode Island showed no significant post-ban trend. For deaths involving illicit opioids specifically, the author reports a significant increase in Indiana, Vermont, and Arkansas, a decrease in Alabama and Rhode Island, and no treatment effect in Wisconsin. Table 3.1 shows crude overdose rates continuing to climb through 2020 in the banning states. This supports Policy Idea 3.2: because access-restricting measures are not reliably followed by improved outcomes, a brief displacement-awareness review before endorsing such measures is prudent.

Author's interpretation and limitations (important — stated on the attached pages). The author does not attribute these outcomes to the bans. On the contrary, the author concludes that other factors — an increase in illicitly manufactured fentanyl, reduced supply of prescription opioids, and the COVID-19 pandemic — had a greater effect on the opioid epidemic than did the kratom legislation, and expressly states that the study "cannot definitively state that state-level kratom bans caused" the observed increase in overdose deaths. The author also notes that only a small proportion of the population uses the substance. Consistent with that framing, this comment relies on the analysis solely as evidence that a ban was not followed by the improvement its proponents sought — not as proof that the ban caused harm, and not to assert displacement as a demonstrated mechanism.

Framing. This exhibit is offered to illustrate that access-restricting measures are not always followed by improved public-health outcomes, and to support a modest procedural recommendation (a displacement-awareness review). It is not offered as proof that any ban caused harm, nor as an allegation of error, negligence, or misconduct by any individual or institution.

Reproduced from the cited dissertation with submitter highlighting for reviewer convenience; underlying text unaltered.

Table 3.1. Number of opioid overdose deaths and crude rates per 100,000** by year for each state with a legislation banning kratom

	Indiana		Vermont		Wisconsin		Arkansas		Alabama		Rhode Island	
	n	**rate**	**n**	**rate**	**n**	**rate**	**n**	**rate**	**n**	**rate**	**n**	**rate**
2005	163	3.5	46	9.5	278	6.6	127	6.1	83	2.4	122	14.8
2006	183	3.9	57	11.7	347	8.2	142	6.7	129	3.7	130	15.7
2007	246	5.2	53	10.8	370	8.7	151	7.0	166	4.7	88	10.7
2008	316	6.6	58	11.8	366	8.5	206	9.5	194	5.4	132	16.0
2009	336	6.9	46	9.3	398	9.2	218	10.0	208	5.7	115	13.9
2010	297	6.1	45	9.1	417	9.6	193	8.8	190	5.2	112	13.5
2011	371	7.5	60	12.0	477	10.9	175	7.9	178	4.8	145	17.4
2012	**389**	**7.9**	57	11.4	493	11.2	178	8.0	173	4.7	141	16.9
2013	380	7.6	**75**	**14.9**	597	13.5	173	7.7	174	4.7	194	23.2
2014	485	9.7	72	14.3	**636**	**14.3**	175	7.7	281	7.5	210	24.9
2015	559	11.1	83	16.4	629	14.1	206	9.1	289	7.7	257	30.4
2016	823	16.3	103	20.4	867	19.3	**173**	**7.6**	**350**	**9.3**	279	32.9
2017	1203	23.6	119	23.5	939	20.8	196	8.5	433	11.5	**280**	**32.9**
2018	1135	22.2	128	25.1	857	18.9	214	9.3	389	10.2	268	31.5
2019	1288	24.9	117	22.9	934	20.5	206	8.9	424	11.1	243	28.4
2020	1949	37.6	164	32.1	1264	27.6	290	12.4	625	16.3	332	38.8
% Increase from 2005-2020	1,096%	974%	257%	238%	355%	318%	128%	103%	103%	579%	172%	162%

*bold indicates year of legislation implementation

**in adults aged 18 years or older

fairly constant over time (e.g., age, race, ethnicity, poverty, education), as their measurements would be very similar both before and after the intervention (109). Potential confounding is limited to factors that are related to the outcome and change after the time of the intervention.

Conclusion

State-level kratom bans in Indiana, Vermont, Wisconsin, Arkansas and Alabama were associated with sustained increases in opioid overdose mortality rates. Despite controlling for the pre-intervention trend, we cannot definitively state that state-level kratom bans caused the significant increase in opioid overdose deaths that were seen in this study. We understand that there are many factors, including social and structural factors, that influence the opioid epidemic and only a small proportion of the population uses kratom (61). However, it is important to note that bans were put into place in an effort to thwart the addictive and dangerous properties of kratom, yet this study has shown that opioid overdose rates continued to increase at alarming levels even with these bans in place. It is essential that policymakers base decisions regarding kratom on data concerning the benefits (e.g., safer alternative to opioids) or potential negative impacts of kratom legality (e.g., delaying research efforts by scientists), and the use of kratom in it's pure, unadulterated form.

Aim 2: Residence in Urban or Rural Counties in relation to Opioid Overdose Mortality in Kentucky before and during the COVID-19 Pandemic

Since the beginning of the epidemic, rates of opioid-related overdose death have differed in rural and urban counties. We examined the association between urban residence and subsequent opioid overdose mortality in Kentucky and whether this association was modified by the COVID-19 pandemic. Prior to the pandemic, hospitalized people from urban counties were more likely to die from an opioid overdose than people living in rural counties. During the pandemic, urban and rural counties became more similar in regard to their association with opioid overdose mortality. The same held true when limiting the analysis to hospitalizations involving an illicit opioid, but not for prescription opioid-related hospitalizations.

Aim 3: Evaluating State-Level Kratom Legislation and Opioid Overdose Mortality in the United States: an interrupted time series analysis

With the rise in opioid overdose deaths, people have sought out alternative substances that are advertised to have less side effects and lower abuse potential, such as kratom. We examined the association between state-level kratom legislation and opioid overdose mortality across US states and found that after controlling for the pre-intervention trend, Indiana, Vermont, Wisconsin, Arkansas and Alabama had higher opioid overdose deaths rates following the kratom ban implementation. Rhode Island did not show a significant trend following the kratom ban; however, there were few points following the ban implementation and this result may not hold with additional years of opioid overdose mortality data. When we limited the analysis to prescription opioid overdose deaths, we observed a decrease in mortality in Wisconsin, Arkansas and Rhode Island, but no effect in Indiana, Vermont or Alabama. In regard to illicit opioids, there was a significant increase in deaths in Indiana, Vermont, and Arkansas, a

significant decrease in deaths in Alabama and Rhode Island, and no observed treatment effect in Wisconsin. These results suggest that there are other interventions, such as an increase in illicitly manufactured fentanyl, reduced supply of prescription opioids, and the COVID-19 pandemic, all of which have had a greater effect on the opioid epidemic than did legislation banning kratom.

Strengths and Limitations

This dissertation has several strengths worth mentioning. One strength is that we considered various classes of opioid overdose deaths. Though prescription and illicit opioid overdoses are closely intertwined, it is important to differentiate the deaths and examine them as distinct epidemics in order to craft more appropriate prevention and response efforts. Therefore, within each aim we looked at the exposure separately for prescription opioids and illicit opioids as well as all opioids combined.

We also chose to follow the Center for Disease Control and Prevention's (CDC) recommendations for quantifying prescription opioid overdoses as deaths involving natural and semisynthetic opioids (i.e., T40.2) and methadone (i.e., T40.3) (21,69). Deaths from fentanyl, whether pharmaceutical or illicitly manufactured, are coded under T40.4 (21,69), and have been traditionally included in the prescription opioid definition. However, there is increasing evidence (21,24,82), including from this dissertation, that the high proportion of fentanyl overdose deaths in recent years is predominantly due to illicitly manufactured fentanyl as opposed to prescription fentanyl; and, the fentanyl epidemic is operating distinctly from the prescription opioid epidemic (23). Using the current conservative approach that separates T40.4 codes from other prescription opioids (T40.2-T40.3) likely provided a more accurate representation of deaths involving prescription opioids.